INSTITUTE: Clinical Center

STUDY NUMBER: 05-CC-0246 PRINCIPAL INVESTIGATOR: Letha Healey, MD

STUDY TITLE: The Evaluation of Focal Contrast-Enhancing Brain Lesions in HIV-Infected Patients

Latest IRB Review: Initial Review 7/11/05
Latest Amendment Approved: Amend C 2/9/06 Date Posted to Web: 2/14/06
Screening Consent

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

You are invited to participate in a voluntary research trial that will examine a method of diagnosing primary central nervous system lymphoma (a type of cancer) in HIV-infected patients. You are eligible for this study because you have been diagnosed as having at least one focal brain lesion (an injury in a specific area of the brain); lymphoma is one of the common causes of such brain lesions in HIV-infected patients. This consent is for the screening portion of the study only, during which we will determine if you are eligible for the primary study.

THE PURPOSE OF THIS STUDY

Focal brain lesions can develop in HIV-infected patients who have low CD4 counts (usually below 200 cells/mm^3). CD4 cells help to fight infections, and they are the main cells destroyed by the HIV virus. The two most common causes of focal brain lesions are toxoplasmic encephalitis (an infection) and primary central nervous system lymphoma.(lymphoma of the brain or spinal cord). Patients with such brain lesions will often experience seizures (convulsions), confusion, personality changes, or headache.

Toxoplasma gondii, which causes toxoplasmic encephalitis, is a parasite that can infect healthy people without making them sick. In immunosuppressed patients (patients whose immune systems have trouble fighting infections) such as HIV-infected patients with low CD4 counts. *Toxoplasma* can cause disease in the brain and other tissues. The infection is treated with antibiotics, and most patients will start to get better within 2 to 4 weeks of starting the medicine.

Primary central nervous system lymphoma (PCNSL) is a relatively rare type of cancer that usually occurs in patients with damaged immune systems, including HIV-infected patients with very low CD4 cell counts. Research has shown that people with PCNSL frequently also have Epstein-Barr virus (EBV) present in the fluid surrounding their brain (spinal fluid). By measuring the amount of genetic material (DNA) related to EBV in the spinal fluid, one can determine whether or not the virus is present. Treatment options for PCNSL include radiation therapy and chemotherapy (cancer-fighting medicines). These treatments appear to work better the sooner they are started after a person starts feeling sick.

It is difficult to tell the difference between toxoplasmosis and PCNSL based on routine radiographic imaging (CT [commuted tomography] or MRI [magnetic resonance imaging] scanning). Radiographic imaging is used to create images (i.e. "Take pictures") of organs such as the brain. In order to be 100% sure that a person has PCNSL, it is necessary to get a biopsy (a small piece of tissue) of that person's brain. While there are simpler ways to try to tell if a person has PCNSL, they are not as accurate as using information from a brain biopsy. Currently, in most medical centers, patients that have focal brain lesions are started on antibiotics for toxoplasmosis and watched to see if they get better – if they do not get any better within 2 to 4 weeks of starting antibiotics, they usually undergo a brain biopsy in order to try to figure out whether they have PCNSL or toxoplasmosis. Thus, several weeks may pass, in which time a patient might get sicker, before it is determined that they have PCNSL.

The primary purpose of this study is to determine if a combination of two tests – a measurement of EBV DNA in the cerebrospinal fluid and FDG-PET scan of the brain –will make it possible to quickly figure out which patients have PCNSL. Patients who are positive for either one, or both of these tests will undergo an immediate brain biopsy, since they are more likely to have PCNSL (and at present it is necessary to look at tissue from a brain biopsy in order to tell if a person has PCNSL). For patients in whom both of these tests are negative, toxoplasmosis therapy (antibiotics) will be continued and a biopsy will be performed only if they do not get any better in 2 to 4 weeks. All patients enrolled in the study will be treated with antiretroviral medications to treat HIV infection. We will also be testing two different nuclear medicine imaging techniques, ^{201}Tl-SPECT and FDG-PET imaging, to see if one is better in distinguishing between toxoplasmosis and PCNSL. By participating in this study, you may have procedures and examinations done that may not be done if you were being evaluated in other medical centers. In some medical centers, not all patients with focal brain lesions have brain biopsies or have either a SPECT scan or a PET scan. While these studies are considered to be the current standard of care for people with brain lesions, you might not have to go through all of these procedures if you were not enrolled in this study.

If PCNSL is diagnosed, all patients will have the opportunity to participate in a companion study being conducted by the National Cancer Institute that is investigating new treatments for PCNSL in HIV-infected patients once this study is open for enrollment. If you are not eligible to participate in that study, you will be referred for treatment by your primary physician or may be eligible for enrollment in another NIH protocol.

Up to one hundred twenty patients will be screened for enrollment in this study.

STUDY ENTRY CRITERIA

Inclusion Criteria:
You may be eligible to participate in this study if you

1. Are at least 18 years old
2. Are willing and able to provide written informed consent, comply with study requirements and procedures, and comply with clinic policies including allowing storage of blood or cerebrospinal samples for use in the future for the study of HIV, AIDS, primary central nervous system lymphoma, toxoplasmic encephalitis, and related diseases. You should also be willing and able to designate a durable Power of Attorney (DPA) to make medical decisions for you. Your Power of Attorney will be able to make medical decisions on your behalf if you are unable to do so on your own. If you are unable to provide written informed consent and you are unable to designate a durable Power of Attorney to make decisions for you, a family member may be appointed as your durable Power of Attorney. An NIH DPA has no standing outside of the NIH and has no power over a patient's money or other assets.
3. Have a history of HIV infection
4. Have evidence of at least one focal enhancing brain lesion seen on MRI or CT scan
5. Are willing to undergo the procedures involved in the diagnostic protocol: lumbar puncture (spinal tap), FDG-PET scan, ^{201}Tl-SPECT scan, brain biopsy (if indicated).
6. Are willing to undergo HLA testing.

You will NOT be eligible to participate in this study if you:

1. Have a prior history of primary central nervous system lymphoma (PCNSL)
2. Are pregnant or breastfeeding
3. Have a history of toxoplasmic encephalitis or other infection of the central nervous system that may cause focal enhancing brain lesions
4. Have a history of any other cancer unless it has been in remission for one year or longer (except non-melanoma skin cancer or Kaposi's sarcoma).
5. Your weight is greater than 400 lb (you will be unable to undergo PET scanning).

STUDY PROCEDURES
During the screening portion of the study, you will undergo several clinical procedures including a medical history, a brief physical examination, and an MRI of the brain with gadolinium. Gadolinium is a contrast agent that is used to help the doctors find the damaged areas of your brain. A CT scan may be performed if an MRI scan is determined not to be in your best medical interest or cannot be obtained. These scans are considered to be the standard procedure done for all patients with brain lesions. Blood will be drawn from your veins (venipuncture) and your blood and urine will be tested for liver and kidney diseases that might exclude you from study participation. Your blood will also be tested for HIV (the virus that causes AIDS) and for the presence of Epstein-Barr virus (EBV). Women will be tested for pregnancy. If you are pregnant, you cannot be in this study because we do not know what effects the study procedures may have on the unborn baby. Other laboratory tests, including research tests, will be run.

MAGNETIC RESONANCE IMAGING (MRI)
During the MRI, you will lie on a table that can slide in and out of a cylinder. You will be in the scanner for about two hours. You may be asked to lie still for up to 10 minutes at a time. While in the scanner you will hear loud knocking noises, and you will wear earplugs to muffle the sound. You will be able to communicate with the MRI staff at all times during your scan, and you may ask to be moved out of the machine at anytime. During the MRI, you will receive a contrast agent (gadolinium) through an intravenous catheter. A needle will be used to guide a thin plastic tube

(catheter) into one of your arm veins. The needle will be removed, leaving only the catheter in the vein. The catheter will be taped to the skin to hold it in place.

If you are eligible based on the results of your screening evaluation, you will be invited to enroll in the study.

HEPATITIS SCREENING

Some of the blood drawn from you as part of this study may be used to screen for different types of viral liver infections, such as hepatitis A, B and C. If the testing shows evidence of an acute or chronic hepatitis, you and your doctor will be informed of the results; we will not provide therapy for hepatitis infection under this protocol. If you do not have a primary care physician, the study team will assist in referring you to an appropriate physician for evaluation.

GENETIC TESTING AND STORED SAMPLES

Genetic Testing

Some of the blood drawn from you as part of this study will be used for genetic testing including HLA typing, which is a genetic test of markers of the immune system. HLA typing is usually used in matching for bone marrow or organ transplants. For research, HLA testing may be used to try to identify factors associated with the progression of HIV disease or related conditions. In addition, determining HLA type is necessary to be able to perform certain research studies. Some HLA types have been associated with an increased risk of certain diseases like arthritis and other rheumatologic problems. However, simply having those HLA types does not mean you will have developed these diseases.

In general, genetic testing may tell researchers something about how health or illness is passed on to you by your parents or from you to your children. When thinking about whether or not to participate in genetic studies, you should consider the possible effects on your emotional well-being. How might you feel about yourself and your life if you learned that you and your children might be at increased risk of some disease, especially if there were no treatment? This could cause stress, anxiety, or depression. Additional genetic counseling and advice are available from the National Institutes of Health to help you understand the nature and implications of the findings for you and your family. Also, relationships with other family members may be affected by finding out risks they have but did not want to know. An example would be if your children, brothers or sisters find out that they have risks for health problems because of information found out about you.

Genetic testing can also be used to determine if people are directly related. These tests sometimes show that people were adopted or that their biological parent is someone other than their legal parent. If these facts were not known previously, they could be troubling. It is our policy not to discuss such information unless it has direct medical or reproductive implications for you or your family. By agreeing to participate in this study, you do not waive any rights that you may have regarding access to and disclosure of your records. For further information on those rights, you can contact the principal investigator of this study.

Any genetic information collected or discovered about you or your family will be confidential. Results of HLA testing will become a part of your medical record at NIH. Medical records containing this information are maintained in a secure manner. Genetic information about you will not be revealed to others, including your relatives, without your permission. We will not release any information about you or your family to any insurance company or employer unless you sign a document allowing release of information. Instances are known in which genetic information has been obtained or requested when a person applies for health insurance or a job.

Stored Samples
We may take extra blood and tissue samples and store them for future research. These samples will help us learn more about HIV, AIDS, primary central nervous system lymphoma, toxoplasmic encephalitis, the immune system, diseases of the central nervous system, or related conditions. In general, the research tests we perform are not like routine medical tests, and may not relate directly to your medical care, so we may not put future test results in your medical record. However, if you wish, someone on the study team will discuss the test results with you. We will not share these test results with your private doctor unless you ask us to do so.

By agreeing to participate in this study, you do not waive any rights that you have regarding access to and disclosure of your records. For further information on those rights, please contact Dr. Letha Healey (PI), Building: 10, Room 8C-313, Telephone: (301) 435-7688.

Labeling of Stored Samples
We will label your stored samples with a code that only the study team can link to you. We will keep any information that can be traced back to you private to the extent permitted by law**.**

Future Studies
Other investigators may want to study your stored samples. If so, the NIH study team may send your samples to them, along with the coded label that can identify you. The study team may also share information such as your gender, age, health history, or ethnicity. In some cases, an Institutional Review Board (IRB) will review new research proposals that would like to use your samples. The IRB is a committee that oversees medical research studies to protect volunteers' rights and welfare.

Investigators will *only* use your samples for research. We will not sell them. Future research that uses your samples may lead to new products, but you will not receive payment for these products. Some future studies may need health information (such as smoking history or present health status) that we don't already have. If so, the NIH study team will contact you for this information.

RISKS AND BENEFITS
Risks Associated with Protocol Screening
Blood Drawing: Possible complications from drawing blood (venipuncture) include pain or bruising at the site of the blood draw, feeling lightheaded, fainting, and rarely, infection. During each venipuncture, approximately one to ten tablespoons of blood will be obtained (15 to 150 ml of blood). The amount of blood drawn will not exceed 30 tablespoons (450 ml) in a six-week period, which is within the safety guidelines set by the Clinical Center of the National Institutes of Health.

Magnetic Resonance Imaging (MRI) Scan: People are at risk for injury from the MRI magnet if they have pacemakers or other implanted electrical devices, brain stimulators, dental implants, aneurysm clips (metal clips on the wall of a large artery), metallic prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, implanted delivery pump, or shrapnel fragments. Welders and metal workers are also at risk for injury because of possible small metal fragments in the eye of which they may be unaware. You will be screened for these conditions prior to the study, and if you have any, you will not receive an MRI scan. If you have a question about any metal objects being present in your body, you should inform the physician. In addition, all magnetic objects (for example, watches, coins, jewelry, and credit cards) must be removed before entering the MRI scanning room. Because pregnancy is a study exclusion, all women of childbearing potential will have a pregnancy test performed, which must be negative, before

proceeding. Individuals with fear of confined spaces may become anxious during an MRI. You will be asked to complete an MRI screening form. There are no known long-term risks or consequences of MRI scans.

Computed Tomography (CT) Scan: CT scan with intravenous contrast will be used only when MRI scan is contraindicated or unavailable. The procedure is painless and takes approximately fifteen minutes. The primary risk is of an allergic reaction to the contrast dye. The chance of a fatal reaction to the contrast is approximately 1 in 100,000. Those with a history of iodine or seafood allergy, who may be at increased risk of an allergic reaction to contrast dye, may require pretreatment with anti-histamine agents and/or corticosteroids. There is a small risk of contrast leaking out side of the vein at the time of injection; large quantities of contrast under the skin may cause skin breakdown.

If you are eligible and decide to enroll in the study for which you are screening, you will be given a detailed explanation of the risks involved and you will need to sign another consent.

Risks Associated with Stored Specimens
The greatest risk is that someone may take information from your medical records without your permission. The chances of this happening are very low. If this information becomes available, you may face discrimination when you apply for insurance or a job. You may also have similar problems if you share the information yourself or let us release your medical records.

Conditions for Withdrawal
You may voluntarily withdraw from this study at any time. Additionally, you may be removed from the study without your consent if it is felt by the principal investigator to be in your best medical interest, if you do not comply with the study requirements, or if the study is cancelled or stopped.

Benefits
The screening tests will not be of direct benefit to you. In general, future research that uses your samples will not help you, but it may help us learn about the presentation, diagnosis, and treatment of brain lesions in patients with HIV or related conditions. This research may also help us learn how to prevent or treat the condition.

Alternatives
Participation in this protocol is voluntary. You can choose not to participate in these screening visits and tests, and you can choose not to allow HIV, hepatitis or HLA testing or storage of blood, in which case you would not be eligible for further participation in the protocol. If you agree to participate in this study, you agree to let us store your samples for future research. You also agree that we can contact you again in the future. No matter what you decide, you may still participate in other studies at NIH. However, your refusal to let us store your samples may lead to your withdrawal from this specific study. Even if you agree now to let us store your samples, you can change your mind later. If you do, please contact us and say that you do not want us to use your samples for future research.

Costs to You For Your Participation
There will be no charge to you or your health insurance company for any of the costs that are directly related to this study. However, the costs of any other medical care during this period will be charged to you or your health insurance.

Remuneration
You will receive no compensation for your participation in this study. Participants may receive partial remuneration for the immediate costs associated with their study-related expenses (travel costs, lodging, etc).

POLICY REGARDING HIV TESTING
As part of your participation in this study, it will be necessary to test your blood for the presence of antibodies to the Human Immunodeficiency Virus (HIV), the virus that causes Acquired Immune Deficiency Syndrome (AIDS). In order to perform the test, a small amount of blood (approximately 2 teaspoons) will be withdrawn from one of your arms with a needle. You may experience some slight discomfort at the needle entry site and there may be some bruising. In addition, there is a very small risk of you fainting or of infection at the needle entry site. If your test results are found to be positive, or if you are otherwise diagnosed as having AIDS, you should be aware of the following Clinical Center HIV Testing Policy:

1. Your physician will notify you promptly of the HIV test results.

2. Your physician and/or the Clinical Center HIV counselor will offer you, and any current and/or ongoing sexual partner(s) (spouses are generally considered to be current or ongoing sexual partners) or needlesharing partner(s) you identify, information on the meaning of the test results and how to prevent the spread of the infection.

3. Because the virus may be transmitted in several ways, it is important that you inform sexual and/or needle-sharing partner(s) that any, or all, of them may have been exposed to the HIV virus and encourage them to be tested. If you request it, staff at the Clinical Center will assist you in notifying your partner(s) and arrange counseling for them through an HIV counselor.

4. The results of your HIV test and/or documentation of the diagnosis of AIDS will become a part of your Clinical Center medical record and, as such, will be protected from unauthorized disclosure by the Federal Privacy Act of 1974. In general, access to your medical record will be restricted to those health care professionals directly involved in your care or in the conduct of ongoing biomedical research, and information is not usually released to other third parties without your permission or that of your designated representative. However, there are some particular routine uses of such information of which you should be aware.

    a. If you are unwilling or unable to notify your partner(s), the Clinical Center is responsible for attempting to contact and inform them of their possible exposure to the virus. Reasonable attempts will be made to protect your identity including withholding your name when notifying any partner(s) of their possible exposure. Some notification or counseling of current and/or ongoing partners may be carried out through arrangements with, or referral to, local public health agencies.

    b. A summary of your care at the Clinical Center will be sent to the physician who referred you here for treatment.

    c. The Clinical Center may report certain communicable diseases, such as HIV infection, to appropriate State and Federal government agencies.

        i. For Clinical Center patients who are Maryland residents, the Clinical Center reports by "Patient Unique Identifier Number" (rather than by name) newly obtained HIV-positive results from its laboratory to the Maryland Department of Health and Mental Hygiene. Patient Unique Identifier

Number is: last four digits of social security number, birth month, birth day, birth year, race and gender.

ii. For Clinical Center patients who are Maryland residents, the Clinical Center reports by name new cases of AIDS to the Maryland Department of Health and Mental Hygiene.

iii. For Clinical Center patients who are not Maryland residents, the Clinical Center reports HIV-positive results and/or AIDS to the patient's primary care/referring physician. If you have any questions regarding the HIV testing or the information provided above, you are encouraged to discuss them with your physician and/or a Clinical Center HIV counselor: (301) 496-2381.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or other authorized people.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Letha Healey, MD, Building: 10, Room 8C-313, Telephone: (301) 435-7688.

You may also call the Clinical Center Patient Representative at 301-496-2626.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/Legal Representative _____ Date _____

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study. (Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/Guardian _____ Date _____

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian _____ Date _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM JULY 11, 2005 THROUGH JULY 11, 2006.

Signature of Investigator _____ Date _____ Signature of Witness _____ Date _____